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Vutrisiran for ATTR-CM: Impacts on Functional Capacity and Quality of Life

Announcer:
This is *On the Frontlines of ATTR-CM* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan Quigley:
You're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and joining me to discuss the HELIOS-B trial, which evaluated the impact of vutrisiran on functional capacity and quality of life in patients with transthyretin amyloidosis with cardiomyopathy, or ATTR-CM for short, is Dr. Farooq Sheikh. Not only is he the Medical Director of the Advanced Heart Failure Program at MedStar Heart and Vascular Institute, but he's also an Associate Professor of Medicine at Georgetown University School of Medicine in Washington, D.C. He's also co-author of this study, which we'll be discussing today.

Dr. Sheikh, welcome to the program.

Dr. Sheikh:
Thank you so much for the introduction. I'm happy to be with you and our audience.

Ryan Quigley:
Absolutely, likewise. Happy to have you with us. So, Dr. Sheikh, let's start by talking about functional capacity, which was measured in HELIOS-B with the six-minute walk test. What makes this test such a valuable clinical tool in ATTR-CM, and why was it chosen as a key endpoint in the study?

Dr. Sheikh:
The six-minute walk test, otherwise known as the six-minute hall walk test, is a test routinely used in the evaluation of patients with heart failure. And in ATTR-CM, we're speaking about a disease that unfortunately—for our patients who suffer from cardiomyopathy—the common theme is heart failure. And this test has been validated in multiple ways. Simply put, I would describe it as a test that is simple to perform, that is reproducible, and that has been shown to be a great assessment of functional capacity, which is important because functional capacity in heart failure predicts a few things. One, it actually predicts long-term survival. It also predicts the risk of hospitalization, which is obviously an adverse event. We want to avoid our patients being hospitalized. But it also predicts other aspects of the patient's life, including their quality of life, as well as other outcomes in the field, so this is a diagnostic test that has great meaning for our patients and for our clinicians.

Ryan Quigley:
And now, if we take a look at the results, what were the differences between vutrisiran and placebo in terms of maintaining or improving six-minute walk test distance at the 30-month mark?

Dr. Sheikh:
The way I would begin is to just briefly describe the HELIOS-B trial, which was published in *The New England Journal*. The analysis we are talking about today is a secondary analysis, which was a pre-specified analysis. So when the trial was designed and those individuals on the steering committee designed the trial, they came up with a number of analyses that they decided would be very important and illustrative in determining the benefits of the therapy, one of which was the question of, as you highlighted in the title, what is the impact of vutrisiran on functional capacity, health status, and quality of life? And ultimately, the goal was to compare both the six-minute walk test as well as some quality-of-life measures—which we'll talk about subsequently—between the two groups from the time they are initially in the trial, randomized to either the active treatment or the placebo, and then at the end of the trial at month 30. And the

goal of this was to actually assess how many patients in each arm of the trial—those receiving vutrisiran and those who were not randomized to vutrisiran—either maintained or improved their functional capacity at 30 months.

And the way we did this was to actually do several subgroup analyses amongst the group. The way it was done was that, based on prior published data in the field of ATTR-CM, multiple publications have highlighted that differences can be seen with measurements of functional capacity distance measured in meters, and that, actually, there was data to say that seven meters is a meaningful number, 15 meters is a meaningful number, and 35 meters is a meaningful number. So the question that was asked by the investigators—which I was very lucky to lead the group in this regard—was, what was that difference? How many patients either maintained or improved their functional capacity at the end of 30 months when you compare those who receive vutrisiran to those who did not?

The improvement was defined by those, where the cutoff of choice—so seven, 15, or 35 meters— was established as those cutoffs based on published data which demonstrated that if it was a seven-meter cutoff, they had to have improved by at least seven meters; if it was a 15-meter cutoff, they had to improve by greater than 15 meters; and then, obviously, subsequently for the latter, the 35 meters. And ultimately, what was demonstrated was that in regard to the six-minute walk distance, there was a much higher proportion of individuals randomized to vutrisiran who met all of those pre-specified subgroups—the ones that were greater than seven, 15 or 35 meters, demonstrating the benefits of vutrisiran in this group.

Ryan Quigley:
And now, Dr. Sheikh, as a follow-up to that, how consistent were these benefits across subgroups, like age, disease type, or tafamidis use?

Dr. Sheikh:
We were able to demonstrate in the manuscript that has been accepted in the *Journal of the American College of Cardiology*—and I encourage the listeners to pull the paper so that they can actually graphically see this, because graphic depiction sometimes is really illustrative in trying to make the point that I'm going to say verbally—that when they were developing and when we developed this analysis, the pre-specified groups were as follows: age and the baseline use of tafamidis. Remember, in the group that did not receive vutrisiran, there was a quote-unquote "true placebo group" that had not received any disease-modifying therapy. Those are patients who just received a placebo. And then there was a group of patients—40 percent in the beginning at the time of enrollment in the trial and another 20 percent who received tafamidis after randomization of the trial—that was the baseline tafamidis group. That group was a pre-specified group as well. The third one was, as you highlighted, Ryan, those that had variant or hereditary amyloid cardiomyopathy versus wild-type disease, and then also stratified for NYHA functional class and the NT-proBNP.

The take-home message, simply put in one sentence, is actually the benefit was garnered by all the groups and it was a very impressive finding. The overall population—just take the entire cohort—the difference in favor of vutrisiran was 26.5 meters. And when you looked at the subgroups, age above 75 or those 75 or younger, the benefits were seen in either one of those groups—the ones who were randomized to vutrisiran, including those who had baseline tafamidis use, and the type of ATTR disease they had. Actually, it also benefitted those people above or below the NT-proBNP cutoff of 2000 nanograms per liter.

Ryan Quigley:
Thank you very much for that, Dr. Sheikh. For those just tuning in, you're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Farooq Sheikh about the effects of vutrisiran on functional capacity and quality of life in ATTR-CM patients.

And now, Dr. Sheikh, I'd like to shift gears now and discuss quality of life, which was measured in HELIOS-B using the Kansas City Cardiomyopathy Questionnaire Overall Summary, or KCCQ-OS. What does this score capture, and why is it such an important endpoint in ATTR-CM trials?

Dr. Sheikh:
Thank you, Ryan. I think analogous to our prior conversation as related to functional capacity, there are several questionnaires that have been validated in the field of heart failure that have been demonstrated to be instruments that can be used to assess quality of life in our patients. In this case, the Kansas City Cardiomyopathy Questionnaire Overall Summary is a well-validated tool, which was developed, not surprisingly, in Kansas City by Dr. John Spertus and colleagues at Mid America Heart Institute, which actually is specific for heart failure. And it consists of 23 individual components that cover multiple domains. In groups we include symptom frequency, symptom burden, physical limitations, social limitations, estimates and features of quality of life, symptom stability, and, actually, self-efficacy. The four larger, broad categories that were the focus of this analysis could be better stated as physical functional score, total symptom score, quality of life score, and social limitation score. And as I mentioned, they have been validated in a number of forms of heart failure, so we were lucky to utilize this well-validated tool to guide us.

We also know that a minimal clinically important difference could be estimated based on published data, which, depending on the domain, would be a difference in five points. The way we think about this is that the test is measured zero to a hundred. A higher score means a better quality of life. And we know that if you're comparing two groups where there's a difference of at least five points, that's the minimal clinically important difference between the groups, and that's what our purpose was in this analysis.

Ryan Quigley:
And now, in terms of results, what kind of quality-of-life improvements were observed in patients on vutrisiran compared to placebo, both overall and in subdomains?

Dr. Sheikh:
Similar to what we did with six-minute walk test, we asked the question when looking at the KCCQ Overall Summary, what was the benefit for patients who received vutrisiran versus placebo or monotherapy? And the overall take-home message here is using the cutoffs of five points or 10 points, the patients who received vutrisiran relative to placebo were more likely to have a higher score at the end of the trial, either by the five-point cutoff or the ten-point cutoff. That's the overall population receiving vutrisiran, including those patients with monotherapy as well. In the baseline tafamidis group, so those who had received baseline tafamidis, there was actually a higher score for those individuals, which is great news for those patients who have been receiving it for an extended period of time consistent with the original phase III clinical trial that demonstrated the benefit. But even numerically in that population, those who received vutrisiran had a higher numerical value receiving that drug relative to placebo.

Ryan Quigley:
Very interesting. Okay. So before we wrap up our program, Dr. Sheikh, let's think about the big picture for a moment. When treating patients with ATTR-CM, why is it important to observe functional capacity and quality of life outcomes alongside traditional objective endpoints?

Dr. Sheikh:
I think this is probably the most important question. And when I was asked to participate in this analysis, I was so excited, because when thinking of our patients—when we sit at their bedside with them and we reflect on their lives and their goals—we're talking about a patient population whose mean age is somewhere between 75 and 77 years of age. This is a population, that, bless them, have lived long lives, and at this point in their life, yes, they want longevity; they want to live longer; but what they really want is to be able to have a better quality of life. And I think most of us as human beings judge that by our functional capacity and then measures of our quality of life. But whether it was the six-minute walk test where patients receiving vutrisiran had better outcomes irrespective of the use of tafamidis, or by the KCCQ Overall Summary, wherein all of the subdomains that follow—which I described earlier in this discussion—patients received the benefit, and their quality of life and their physical capacity to do things improved when they received vutrisiran.

What is exciting is that there was concordance amongst all the subgroups. And the patients numerically had objective evidence of improvements in their quality of life, which again, in this patient population is very meaningful, because I think for those of us who are lucky enough to take care of amyloidosis patients, we recognize that's something that is really driving their need and their desire to find better therapies to improve their life.

Ryan Quigley:
With those closing thoughts in mind, I want to thank my guest, Dr. Farooq Sheikh, for joining me to discuss how vutrisiran affects functional capacity and quality of life for patients with ATTR-CM.

Dr. Sheikh, it was great having you on the program today.

Dr. Sheikh:
Thank you so much for the invitation, and I look forward to future discussions.

Announcer:
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